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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/17/2003

23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/589,870	GOSHORN ET AL.	
	Examin r	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-22,24-39 and 65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-22,24-39 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed July 10, 2003 in Paper No. 22 is acknowledged and has been entered. Claims 18 and 24 have been amended.

2. The declaration under 37 CFR § 1.132 by Stephen C. Goshorn is acknowledged and has been entered.

3. Claims 18-22, 24-39, and 65 are pending in the application and are currently under prosecution.

Grounds of Claim Rejections Withdrawn

4. Unless specifically reiterated below, the grounds of claim rejections set forth in the previous Office action mailed January 13, 2003 (Paper No. 20) have been withdrawn.

Response to Declaration under 37 CFR § 1.132

5. The declaration under 37 CFR § 1.132 by Stephen C. Goshorn is insufficient to overcome the rejection of claims 18-22, 24-32, 38, 39, and 65 under 35 U.S.C. 103(a) for the reasons set forth below. The particular reasons have been set forth below as part of the response to Applicants' remarks.

Claim Objections

6. Claim 39 is objected to because of the recitation of improper Markush language. Claim 39 should be amended to delete "or" and to recite instead "and" in line 3.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 33-37 and 65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 33-37 and 65 are indefinite because claim 33 depends from claim 23, which has been canceled, and claims 34-37 and 65 depend from claim 33. The metes and bounds of the claimed subject matter cannot be ascertained and therefore claims 33-37 have not been further considered upon he merits. Claim 65 has been further considered, but only to the extent that the claim is dependent upon any one of claims 18-22, 24-32, 38, and 39.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

11. Claims 18-22, 24, 26, 28, 38, 39, and 65 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 6,451,995 B1.

US Patent No. 6,451,995 B1 ('995) teaches a fusion protein as recited in claims 18 and 26, and a composition thereof as recited in claim 65, wherein said fusion protein comprises at least a first and a second polypeptide joined end to end, wherein the first polypeptide is

streptavidin and wherein said second polypeptide is a single-chain antibody, wherein said first and second polypeptides are separated by a linker of at least 2 or at least 4 amino acids, as recited in claims 19 and 20, respectively, and wherein said linker consists of between 4 and 20 amino acids, as recited in claim 21. The fusion protein of '995 comprises at least amino acids 25-182, 29 to 182, 38 to 174, 38 to 175, 38 to 176, 38 to 177, 38 to 178, 38 to 179, 38 to 180, 38 to 181, or 38 to 182 of streptavidin, as recited in claims 38 and 39, because the fusion protein comprises streptavidin; see claims 4 and 7 of the prior art. '995 teaches the fusion protein is capable of forming a tetrameric complex with a second, third, and fourth fusion protein, as recited in claim 24. The single-chain Fv antibody of the fusion protein of '995 comprises a linker, which connects the variable light and variable heavy chains, as recited in claim 28. See the entire document; see the previous Office action mailed January 13, 2003 (Paper No. 20).

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 18-21, 24, 26, 28, 29, 30, and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dubel et al. (*Journal of Immunological Methods* **178**: 201-209, 1995), as evidenced by Kipriyanov et al. (*Human Antibodies and Hybridomas* **6**: 93-101, 1995), in view of Gallizia et al. (*Protein Expression and Purification* **14**: 192-196, 1998).

Claims 18-21 are drawn to a fusion protein comprising at least a first and a second polypeptide joined end to end, wherein the first polypeptide comprises at least 129 amino acids of streptavidin and wherein said second polypeptide is an antibody or antigen-binding fragment thereof (claim 18), wherein said first and second polypeptides are separated by a linker of at least 2 or 4 amino acids (claims 19 and 20, respectively), or wherein said linker consists of between 4 and 20 amino acids (claims 21). Claim 24, 26, 28, 29, and 30 are drawn to the fusion protein of claim 18, wherein said fusion protein is capable of forming a tetrameric complex with a second,

third, and fourth fusion protein (claim 24), or wherein said antibody is a single-chain Fv antibody fragment (claim 26), or wherein a linker connects the variable light and variable heavy chains of the single-chain antibody (claim 28), wherein the linker comprises at least 10 or 15 amino acids (claims 29 and 30, respectively). Claim 65 is drawn to a composition comprising the fusion protein of any one of claims 18-21, 24, 26, 28, 29, and 30.

Dubel et al. teaches a fusion protein, and a composition thereof as recited in claim 65, comprising at least a first and a second polypeptide joined end to end, wherein the first polypeptide comprises a portion of genomic streptavidin and wherein said second polypeptide is an antibody or antigen-binding fragment thereof, wherein said first and second polypeptides are separated by a linker of at least 2 or at least 4 amino acids, as recited in claims 19 and 20, respectively, and wherein said linker consists of between 4 and 20 amino acids, as recited in claim 21. Dubel et al. teaches the fusion protein is capable of forming a tetrameric complex with a second, third, and fourth fusion protein, as recited in claim 24. The fusion protein of Dubel et al. comprises a single-chain Fv antibody fragment, as recited in claim 26, in which a linker connects the variable light and variable heavy chains, as recited in claim 28. As evidenced by Kipriyanov et al., a linker of 15 amino acids adjoins the variable light chain and variable heavy chain of the single-chain antibody of the fusion protein of Dubel et al., as recited in claims 29 and 30. See the entire document; see the previous Office action mailed January 13, 2003 (Paper No. 20).

The first polypeptide of the fusion protein of Dubel et al. consists of 126 amino acids of streptavidin.

Dubel et al. does not expressly teach that the first polypeptide of the fusion protein can comprise at least 129 amino acids of streptavidin, as set forth in SEQ ID NO: 2.

Gallizia et al. teaches a fusion protein comprising residues 15 to 159 of streptavidin, which is expressed in *E. coli* as a soluble protein. Gallizia et al. discloses that streptavidin is generally expressed in *E. coli* as an insoluble protein; therefore, Gallizia et al. teaches that a recombinant streptavidin molecule in which the first N-terminal residues are substituted with the T7-tag peptide can be used advantageously, because it can be produced in *E. coli* as a soluble and functional protein, which can be purified in two simple steps with yields of 70 mg per liter of

culture. See the entire document; see the previous Office action mailed January 13, 2003 (Paper No. 20).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have replaced core streptavidin of the fusion protein of Dubel et al. with the recombinant streptavidin molecule of Gallizia et al., because Gallizia et al. discloses a recombinant streptavidin molecule in which the first N-terminal residues are substituted with the T7-tag peptide can be used advantageously, since it can be produced in *E. coli* as a soluble and functional protein. One of ordinary skill in the art at the time the invention was made would have been motivated to make the replacement because the teachings of Gallizia et al. suggest that the making the replacement would be advantageous.

14. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dubel et al. (*Journal of Immunological Methods* **178**: 201-209, 1995), as evidenced by Kipriyanov et al. (*Human Antibodies and Hybridomas* **6**: 93-101, 1995), in view of Gallizia et al. (*Protein Expression and Purification* **14**: 192-196, 1998), as applied to claims 18-21, 24, 26, 28, 29, 30, and 65 above, and further in view of Goshorn et al. (*Cancer Research* **53**: 2123-2127, 1993).

Dubel et al. and Gallizia et al. teach that which is set forth in the rejection of claims 18-21, 24, 26, 28, 29, 30, and 65 above.

The first and second polypeptides of the fusion protein of Dubel et al. are adjoined by a linker, which consists of 5 amino acids.

However, neither Dubel et al. nor Gallizia et al. expressly teach or suggest that the fusion protein can comprise a first and second polypeptide adjoined by a linker of between 5 and 10 amino acids.

Goshorn et al. teaches a fusion protein comprising a first and second polypeptide, which are joined by a linker of 6 amino acids. Goshorn et al. teach that the fusion protein is able to bind specifically to tumor cells displaying the antigen to which the antibody from which the fusion protein is derived binds. Goshorn et al. also teach that the second polypeptide of which the fusion protein is comprised retains its capacity to bind substrate. Furthermore, Goshorn et al. teach that "a promising new approach for tumor therapy is to use the antigen-binding capability of an antibody to deliver enzymatic activities to tumor tissues, which are then exploited to

convert relatively nontoxic prodrugs into more active chemotherapeutic agents" (page 2123, column 1). See the entire document; see the previous Office action mailed January 13, 2003 (Paper No. 20).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Dubel et al. to produce and use a fusion protein comprising a first polypeptide and a second polypeptide, wherein the first and second polypeptides are separated by a linker that is between five and ten amino acids, because Goshorn et al. teach that a fusion protein comprising a first and a second polypeptide can be produced, wherein the first and second polypeptides are separated by a linker of 6 amino acids, which retains the ability to bind specifically to the antigen to which the antibody from the which the fusion protein is derived binds and which retains the ability to bind specifically to the substrate to which the second polypeptide from which the fusion protein is derived binds. One of ordinary skill in the art at the time the invention was made would have recognized the equivalency of a linker consisting of 5 amino acids and a linker consisting of 6 amino acids, because the prior art teaches that either a linker consisting of 5 amino acids or a linker consisting of 6 amino acids is suitable for use in the fusion protein. See MPEP §§ 2144.06 and 2144.07.

15. Claims 25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dubel et al. (*Journal of Immunological Methods* **178**: 201-209, 1995), as evidenced by Kipriyanov et al. (*Human Antibodies and Hybridomas* **6**: 93-101, 1995), in view of Gallizia et al. (*Protein Expression and Purification* **14**: 192-196, 1998), as applied to claims 18-21, 24, 26, 28, 29, 30, and 65 above, and further in view of Ohno et al. (*DNA and Cell Biology* **15**: 401-406, 1996, McLaughlin et al. (*Oncology* **12**: 1763-1769, 1998), and the Internet edition of the Bioprobe BV Catalog of Mouse Hybridomas (Bandung, Indonesia).

Dubel et al. and Gallizia et al. teach that which is set forth in the rejection of claims 18-21, 24, 26, 28, 29, 30, and 65 above. In addition, Dubel et al. teaches that single-chain Fv antibodies (scFv) "represent potentially very useful molecules for the targeted delivery of drugs, toxins, or radionuclides to a tumour site" (page 201, column 2). Dubel et al. discloses, "various heterologous protein moieties can also be genetically fused to scFv antibodies to generate bifunctional fusion proteins" (page 202, column 1). Additionally, Dubel et al. teaches that

streptavidin "exhibits one of the strongest noncovalent binding affinities known for a biomolecule", namely biotin (page 208, column 1). Dubel et al. teaches that the fusion protein comprising a single-chain antibody and streptavidin might be "usefully employed for the in vitro purging of autologous bone marrow transplants to eliminate B lymphocytes in the treatment of leukemias and malignant lymphomas" (page 208, column 1).

The single-chain antibody of the fusion protein of Dubel et al. is derived from a monoclonal antibody that binds the "215" epitope of *D. melanogaster* RNA polymerase II.

However, neither Dubel et al. nor Gallizia et al. expressly teach or suggest that the fusion protein can comprise an antibody or antigen-binding fragment thereof, wherein said antibody is monoclonal antibody B9E9, or a single-chain Fv fragment derived therefrom.

McLaughlin et al. teaches that CD20 is an appealing target for a therapeutic antibody, because it is expressed on B cells, and progenitors thereof, from the pre-B cell stage to the activated B cell stage, but not on stem cells, normal plasma cells, or cells of other lineages. McLaughlin et al. discloses that CD20 is expressed on most B cell lymphomas and chronic lymphocytic leukemias and on 50% of pre-B cell acute lymphoblastic leukemias. McLaughlin et al. teaches the clinical status and optimal use of Rituximab™, a recombinant humanized monoclonal antibody that specifically binds CD20 (abstract). Mclaughlin et al. discloses, "as the first MoAb [monoclonal antibody] to gain FDA approval for the treatment of a malignancy, rituximab signals the beginning of a promising new era in cancer therapy" (abstract). McLaughlin et al. teaches the chimeric antibody inhibits the growth of cancer cells expressing CD20 by a mechanism involving complement-dependent cytotoxicity. McLaughlin et al. also discloses that the antibody sensitizes cancer cells to the cytotoxic effects of drugs and toxins. See the entire document; see the previous Office action mailed January 13, 2003 (Paper No. 20).

The Bioprobe BV catalog demonstrates that the hybridoma that produces the anti-CD20 monoclonal antibody B9E9 is commercially available. See page 5 of the Internet published catalog; see the previous Office action mailed January 13, 2003 (Paper No. 20).

Ohno et al. teaches that tissue-specific delivery of a variety of molecules is a valuable technique for medical research (abstract). Ohno et al. discloses, "the cell-targeting moiety can be either antibodies or protein ligands (growth factors) that recognize the corresponding antigens or receptor (page 401, column 1). Ohno et al. demonstrates a streptavidin-ligand fusion protein,

ST-TGF-α, can efficiently target biotinylated protein to cells that express the ligand's receptor. Ohno et al. teaches that streptavidin-ligand and streptavidin-antibody fusion proteins have a number or advantages over immunotoxins and recombinant toxins for treatment of disease, namely cancer. Ohno et al. discloses: "Because biotin can be easily incorporated into a wide range of macromolecules without interfering with biological activities (Wilchek and Bayer, 1990) steptavidin containing-proteins such as ST-TGF-α have wider applicability as bridges to deliver specific molecules such as toxins" (page 405, column 1). Then, Ohno et al. teaches, "other chimeric molecules in which the TGF-α moiety has been replaced by an alternate targeting element may have equally broad applicability to targeting a variety of cell types with equal affinities" (page 405, column 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the fusion protein of Dubel et al. to produce a fusion protein comprising a first polypeptide and a second polypeptide, wherein the first polypeptide is single-chain Fv antibody derived from monoclonal antibody B9E9, because monoclonal antibody B9E9 specifically binds CD20 and is commercially available and easily obtained. One of ordinary skill in the art would have appreciated the fact that, based upon the teachings of Dubel et al., McLaughlin et al., and Ohno et al., the fusion of an antigen-binding fragment of the monoclonal antibody B9E9 and streptavidin could be used simultaneously to inhibit the growth of cancer cells expressing CD20 by a mechanism involving complement-dependent cytotoxicity and to selectively and specifically target biotin-conjugated drugs, toxins, or radionuclides to a CD20+ lymphoma tumor cell, because McLaughlin et al. teach that anti-CD20 antibody-directed therapy can be used effectively to treat patients diagnosed with lymphoma, because Dubel et al. and Ohno et al. teach or suggest the utility of targeting drugs, toxins, or radionuclides to cancer cells using single-chain antibody fusion proteins comprising streptavidin, and finally because McLaughlin et al. teaches that an anti-CD20 antibody can sensitize cancer cells to the cytotoxic effects of drugs and toxins. One of ordinary skill in the art would have been motivated have modified the fusion protein of Dubel et al. in this manner to treat lymphoma, for example.

16. Claims 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dubel et al. (*Journal of Immunological Methods* **178**: 201-209, 1995), as evidenced by Kipriyanov et al. (*Human Antibodies and Hybridomas* **6**: 93-101, 1995), in view of Gallizia et al. (*Protein Expression and Purification* **14**: 192-196, 1998), as applied to claims 18-21, 24, 26, 28, 29, 30, and 65 above, and further in view of Desplancq et al. (*Protein Engineering* **7**: 1027-1033, 1994).

Dubel et al. and Gallizia et al. teach that which is set forth in the rejection of claims 18-21, 24, 26, 28, 29, 30, and 65 above.

The linker adjoining the variable light chain and the variable heavy chain of the single-chain antibody of the fusion protein of Dubel et al. consists of 15 amino acids.

However, neither Dubel et al. nor Gallizia et al. expressly teach or suggest that the fusion protein can comprise an antibody or antigen-binding fragment thereof, wherein said antibody is a single-chain Fv fragment comprising a variable light chain and the variable heavy chain of the single-chain antibody, which are adjoined by a linker comprising at least 20 amino acids, wherein said linker is at least four repeats of SEQ ID NO: 47.

Desplancq et al. teaches, "thirteen scFv variants with linkers comprising up to six repeats of the motif Gly-Gly-Gly-Gly-Ser [SEQ ID NO: 47] were studied" (abstract). Desplancq et al. discloses, "the V_L-linker-V_H variant with a 30 amino acid linker showed slightly poorer binding activity than the monovalent F(ab') standard" (page 1030, column 2). Desplancq et al. teaches, "precipitation problems can be overcome by utilizing longer linkers" (page 1033, column 1). Desplancq et al. also teach that single-chain Fv antibodies "are of interest for clinical applications because their pharmacokinetics and biodistribution may be superior to those of whole antibodies in some clinical applications" (page 1027, column 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the fusion protein of Dubel et al. to produce a fusion protein comprising a first polypeptide and a second polypeptide, wherein the first polypeptide is single-chain Fv antibody comprising a variable light chain and a variable heavy chain of the single-chain antibody, which are adjoined by a linker comprising at least 20 amino acids, wherein said linker is at least four repeats of SEQ ID NO: 47, because Desplancq et al. teaches that single-chain antibodies can be produced in which the variable light chain and the variable heavy chain of the single-chain antibody is adjoined by a linker comprising at least 20 amino acids, wherein

said linker is at least four repeats of SEQ ID NO: 47, such that the resultant antibody is more soluble compared to an antibody having a relatively shorter linker. One of ordinary skill in the art would have been motivated at the time the invention was made to separate the variable heavy and light chains of the single-chain Fv antibody by a linker consisting of at least four gly-gly-gly-gly-ser (SEQ ID NO: 47) linkers, because Desplancq et al. teaches that problems with precipitation, which are encountered during the manufacture of recombinant antibodies, might be overcome by the use of a longer linker separating the variable heavy and light chains of the scFv antibody.

17. Claims 18-22, 24, 26, 28-32, 38, 39, and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,451,995 B1 in view of Desplancq et al. (*Protein Engineering* 7: 1027-1033, 1994).

US Patent No. 6,451,995 B1 teaches that which is set forth in the rejection under 35 USC § 102(e) of claims 18-21, 24, 26, 28, 29, 30, and 65 above.

US Patent No. 6,451,995 B1 does not expressly teach or suggest that the fusion protein can comprise a single-chain Fv fragment comprising a variable light chain and the variable heavy chain of the single-chain antibody, which are adjoined by a linker comprising at least 10 amino acids, as recited in claims 29-31, wherein said linker is at least four repeats of SEQ ID NO: 47, as recited in claim 32.

Desplancq et al. teaches, "thirteen scFv variants with linkers comprising up to six repeats of the motif Gly-Gly-Gly-Gly-Ser [SEQ ID NO: 47] were studied" (abstract). Desplancq et al. discloses, "the V_L-linker-V_H variant with a 30 amino acid linker showed slightly poorer binding activity than the monovalent F(ab') standard" (page 1030, column 2). Desplancq et al. teaches, "precipitation problems can be overcome by utilizing longer linkers" (page 1033, column 1). Desplancq et al. also teach that single-chain Fv antibodies "are of interest for clinical applications because their pharmacokinetics and biodistribution may be superior to those of whole antibodies in some clinical applications" (page 1027, column 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to manufacture the fusion protein of '995 using a single-chain Fv antibody comprising a variable light chain and a variable heavy chain of the single-chain antibody, which

are adjoined by a linker comprising at least 20 amino acids, wherein said linker is at least four repeats of SEQ ID NO: 47, because Desplancq et al. teaches that single-chain antibodies can be produced in which the variable light chain and the variable heavy chain of the single-chain antibody is adjoined by a linker comprising at least 20 amino acids, wherein said linker is at least four repeats of SEQ ID NO: 47, such that the resultant antibody is more soluble compared to an antibody having a relatively shorter linker. One of ordinary skill in the art would have been motivated at the time the invention was made to have done so, because Desplancq et al. teaches that problems with precipitation, which are encountered during the manufacture of recombinant antibodies, might be overcome by the use of a longer linker separating the variable heavy and light chains of the scFv antibody.

Response to Applicants' Remarks

18. In the previous Office action mailed January 13, 2003 (Paper No. 20), claims 18-22, 24-31, 38, 39, and 65 were rejected under 35 U.S.C. 103(a) as being unpatentable over Dubel et al. (*Journal of Immunological Methods* **178**: 201-209, 1995; Form PTO-1449, Paper No. 6, page 3), as evidenced by Kipriyanov et al. (*Human Antibodies and Hybridomas* **6**: 93-101, 1995; Form PTO-1449, Paper No. 6, page 4), in view of Desplancq et al. (*Protein Engineering* **7**: 1027-1033, 1994; Form PTO-1449, Paper No. 6, page 3), Anderson et al. (*Clinical Immunology and Immunopathology* **84**: 73-84, 1997), McLaughlin et al. (*Oncology* **12**: 1763-1769, 1998), the Internet edition of the Bioprobe BV Catalog of Mouse Hybridomas (Bandung, Indonesia), Gallizia et al. (*Protein Expression and Purification* **14**: 192-196, 1998; Form PTO-1449, Paper No. 6, page 3), and Pahler et al. (*Journal of Biological Chemistry* **262**: 13933-13937, 1987), Aragarana et al. (*Nucleic Acids Research* **14**: 1871-1882, 1986; Form PTO-1449, Paper No. 6, page 1), Ohno et al. (*DNA and Cell Biology* **15**: 401-406, 1996; Form PTO-1449, Paper No. 6, page 5), and Goshorn et al. (*Cancer Research* **53**: 2123-2127, 1993; Form PTO-1449, Paper No. 6, page 3). This rejection has been withdrawn in favor of the rejection set forth above; nevertheless, it is noted that Applicants traversed this ground of rejection, arguing the following:

(1) Aragarana et al. and Pahler et al. disclose that the N-terminal and C-terminal amino acids of streptavidin can be discarded without consequence to the biotin-binding activity of protein. Furthermore, Pahler et al. discloses that "core streptavidin" is more soluble than the

parent molecule. Therefore, Aragarana et al. and Pahler et al. teach away from the claimed invention.

(2) The use of "genomic streptavidin" in fusion proteins remedies a shortcoming of using "core streptavidin" in fusion proteins. Moreover, "genomic streptavidin" fusion proteins provide substantial and heretofore unrecognized advantages over "core streptavidin" fusion proteins, including protein folding and secretion into the periplasmic space, which circumvent the need to extract the protein from the cytoplasm, as necessary for "core streptavidin" fusion proteins. Such unexpected findings render the claimed invention non-obvious.

The declaration under 37 CFR § 1.132 by Stephen C. Goshorn states that evidence is described therein, which shows that the instant invention comprising "genomic streptavidin" fusion proteins provides unexpected advantages over the fusion proteins comprising "core streptavidin". The declaration states, prior to the disclosure of the instant invention, preparations of streptavidin expressed gene fusions have been made by expressing a core streptavidin-containing construct in bacteria, wherein inclusion bodies are formed. Such production has several disadvantages, including rigor and expense. The instant invention provides unexpected advantages, as "genomic streptavidin" fusion proteins are expressed as a soluble protein in bacteria and undergo spontaneous folding in the periplasmic space of bacteria.

The declaration further states, nowhere is the use of genomic streptavidin in fusion proteins described or suggested in the cited prior art. Dubel et al. and Pahler et al. describe only the use of "core streptavidin"; and Pahler et al. teaches away from the use of parent streptavidin molecule in fusion proteins, because Pahler et al. discloses that "core streptavidin" is more soluble than the parent molecule.

Applicants' arguments and the merit of the declaration under 37 CFR § 1.132 by Stephen C. Goshorn have been carefully considered but not found persuasive or sufficient to overcome the grounds of rejection under 35 USC § 103(a) set forth above in this Office action.

(1) In reply to Applicants' argument that Aragarana et al. and Pahler et al. teach away from the claimed invention, because the references teach that some N-terminal and C-terminal amino acids of streptavidin are nonessential to the biotin binding activity of the protein, the claims are drawn to a fusion protein comprising at least 129 amino acids of streptavidin, which

has the amino acid sequence set forth as SEQ ID NO: 2. The amino acid sequence of SEQ ID NO: 2 consists of 183 amino acids; therefore, the claims encompass a genus of fusion proteins comprising a truncated streptavidin molecule having at least 129 amino acids of SEQ ID NO: 2, of which at least some of the N-terminal or C-terminal amino acids, or both, can have been deleted. Although the claims do not require the members of the genus of truncated streptavidin molecules to retain the ability to bind biotin, the disclosed utility of the claimed invention depends upon the retention of the biotin-binding activity of the parent molecule. For these reasons, Aragarana et al. and Pahler et al. do not teach away from the claimed invention, because as Applicants have remarked, "the Aragarana *et al.* and Pahler *et al.* references disclose that N-terminal and C-terminal amino acids of streptavidin can be discarded without streptavidin loss of ability to bind biotin" (Paper No. 22, page 9, paragraph 3). Aragarana et al. teaches that the first 24 N-terminal amino acids of the streptavidin gene product compose a signal sequence, which is cleaved during protein maturation to yield a fully functional protein. Pahler et al. teach that the next 13 N-terminal amino acids can be removed without consequence to the protein's ability to bind biotin. Therefore, Aragarana et al. and Pahler et al. provide the suggestion that the claimed invention, i.e., a fusion protein comprising at least 129 amino acids of SEQ ID NO: 2, will retain the ability to bind biotin.

In further reply to Applicants' argument that Pahler et al. teaches away from the claimed invention, because Pahler et al. discloses that "core streptavidin" is more soluble than the parent molecule, Pahler et al. discloses the preparation of streptavidin used, which was supplied as a gift from Apcel Ltd., is a heterogeneous mix of proteins of different sizes processed by an undisclosed protocol, retaining the ability to bind biotin. Pahler et al. discloses that the material has been characterized to find that oligopeptides have been removed from both ends of the initial gene product of 159 amino acids. Because the material retains the ability to bind biotin, Pahler et al. designates this material "core streptavidin". Pahler et al. discloses that the heterogeneity observed in "core streptavidin" most probably derives from uncorrelated double cuts at both ends of the parental molecule, which give rise to four distinct polypeptide chains. Although Pahler et al. discloses that this preparation of streptavidin is more soluble than parental streptavidin, Pahler et al. does not suggest that the parent streptavidin molecule could not be used in a fusion protein. Furthermore, it is unclear whether the observed difference in solubility results from the methods

by which the materials were prepared, but moreover, it is unclear whether a fusion protein comprising any one of the four species of truncated streptavidin molecules of which Pahler et al. discloses "core streptavidin" is probably composed, which is produced using recombinant DNA technology, would be more or less insoluble than a fusion protein comprising the parental molecule, which is produced using this same methodology. Guan et al. (*Appl. Microbiol. Biotechnol.* **44**: 753-758, 1996) teaches that when the streptavidin gene form *S. avidinii* was expressed in *E. coli* as a non-fusion protein, the streptavidin protein accumulated primarily in inclusion bodies; but Guan et al. discloses that a fusion protein comprising streptavidin is expressed *as soluble protein* in *E. coli*.

Nevertheless, the Examiner disagrees with Applicants' assertion that the teachings of Pahler et al. "teach away" from the claimed invention. Pahler et al. is cited as a basis of rejection because in particular, Pahler et al. teaches that the N-terminus of the parental streptavidin molecule is susceptible to protease at or near amino acid residue 14. Therefore, Pahler et al. provides the suggestion that a truncated streptavidin molecule, which retains the ability to bind biotin, would not be susceptible to protease. Thus, Pahler et al. provides the suggestion that a fusion protein comprising an N-terminally truncated streptavidin molecule can be used advantageously over a fusion protein comprising *the parental molecule*, which is susceptible to proteolytic degradation.

The claims are drawn to a genus of fusion proteins comprising streptavidin, or a truncated streptavidin molecule having at least 129 amino acids of SEQ ID NO: 2, of which at least some of the N-terminal or C-terminal amino acids, or both, can have been deleted. Moreover, the claims are not limited to a fusion protein comprising parental streptavidin, as defined by Pahler et al.; nor art the claims limited to a fusion protein comprising the polypeptide of SEQ ID NO: 2.

In still further reply to Applicants' argument that Pahler et al. teaches away from the claimed invention, because Pahler et al. discloses that "core streptavidin" is more soluble than the parent molecule, it is aptly noted that Gallizia et al. teaches a fusion protein comprising a truncated streptavidin molecule of amino acid residues 15-159, which retains the ability to bind biotin and is expressed *as a soluble protein* in *E. coli*. Gallizia et al. discloses that the protein can be purified in two simple steps that can yield up to 70 milligrams of protein per liter of bacterial culture. Gallizia et al. disclose that their methodology appears to be an improvement

over the other reported methods of recombinant streptavidin production.

(2) In reply to Applicants' argument that the use of "genomic streptavidin" in fusion proteins remedies a shortcoming of using "core streptavidin" in fusion proteins because fusion proteins comprising "genomic streptavidin" have a heretofore unrecognized advantage, firstly, it is again aptly noted that the claims encompass fusion proteins comprising at least 129 amino acids of SEQ ID NO: 2 and are not limited to fusion proteins comprising the polypeptide of SEQ ID NO: 2. Secondly, Gallizia et al. teaches a fusion protein comprising a truncated streptavidin molecule of amino acid residues 15-159, which retains the ability to bind biotin and is expressed *as a soluble protein* in *E. coli*. Therefore, the remedy to which Applicants have referred had been recognized and was appreciated at the time the application was filed.

The declaration under 37 CFR § 1.132 by Stephen C. Goshorn states that evidence is described therein, which shows that the instant invention comprising "genomic streptavidin" fusion proteins provides unexpected advantages over the fusion proteins comprising "core streptavidin"; however, no factual evidence has been provided, which supports this assertion.

The declaration states, prior to the disclosure of the instant invention, preparations of streptavidin expressed gene fusions have been made by expressing a core streptavidin-containing construct in bacteria, wherein inclusion bodies are formed. However, to the contrary, as noted above, the prior art teaches that fusion proteins comprising at least 129 amino acids of SEQ ID NO: 2 can be expressed in *E. coli* as a soluble protein.

The declaration further states, nowhere is the use of "genomic streptavidin" in fusion proteins described or suggested in the cited prior art. In reply, again, Gallizia et al. teaches a fusion protein comprising a truncated streptavidin molecule of amino acid residues 15-159, which retains the ability to bind biotin and is expressed *as a soluble protein* in *E. coli*. Additionally, as also noted above, Guan et al. teaches a fusion protein comprising streptavidin is expressed *as soluble protein* in *E. coli*. Therefore, to the contrary of the declaration, the use of "genomic streptavidin" in fusion proteins had been described and it was known that these fusion proteins could be expressed as soluble proteins in bacteria. In addition, it is duly noted at page 94 Kipriyanov et al. (*Hum. Antibodies Hybridomas* **6**: 93-101, 1995) discloses that a single-chain antibody-core streptavidin fusion protein is expressed as a soluble protein in the periplasm of *E. coli*; this disclosure appears to contradict statements in the declaration at page 2 that suggest

fusion proteins comprising core streptavidin form inclusion bodies upon expression in bacteria.

The declaration states Dubel et al. and Pahler et al. describe only the use of "core streptavidin". In response, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The declaration states Pahler et al. teaches away from the use of parent streptavidin molecule in fusion proteins, because Pahler et al. discloses that "core streptavidin" is more soluble than the parent molecule. In reply, Pahler et al. provides the suggestion that a truncated streptavidin molecule, which retains the ability to bind biotin, would not be susceptible to protease. Thus, Pahler et al. provides the suggestion that a fusion protein comprising an N-terminally truncated streptavidin molecule can be used advantageously over a fusion protein comprising *the parental molecule*, which is susceptible to proteolytic degradation.

Double Patenting

19. The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper time-wise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR § 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 18-22, 26, 28, 33-39, and 65 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17-26 and 71-80 of co-pending Application No. 10/150,762. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of claims 17-26 and 71-80 of co-pending Application No. 10/150,762 is encompassed by claims 18-22, 26, 28, 33-39, and 65 of this application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants have requested that this issue be held in abeyance until allowable subject matter is identified.

21. Claims 18-22, 24-39, and 65 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-42 and 77-81 of co-pending Application No. 10/013,173. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of claims 18-42 and 77-81 of co-pending Application No. 10/013,173 is encompassed by claims 18-22, 24-39, and 65 of this application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants have requested that this issue be held in abeyance until allowable subject matter is identified.

Conclusion

22. No claims are allowed.

23. The prior art made of record and not relied upon is considered pertinent to Applicants' disclosure. US Patent Nos. 5,837,814 A, 5,939,531 A, and 5,571,894 A teach fusion proteins comprising antibodies and streptavidin.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached at (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
December 15, 2003